WYETH-AYERST RESEARCH

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August 27, 1999

Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1-23
5630 Fishers Lane
Rockville, MD 20852

Re: {Docket No. 99D-0529}
Draft Guidance for Industry on Changes to an Approved NDA or ANDA

Dear Sir or Madam:

On behalf of American Home Products, a diversified manufacturer of pharmaceutical, over-the-counter and biological drug products, we welcome the opportunity to comment on the draft guidance for industry entitled "Changes to an Approved NDA or ANDA." This letter represents the combined comments of Wyeth-Ayerst Laboratories, Wyeth-Ayerst Research, Whitehall-Robins Health Care, ESI-Lederle, Wyeth-Lederle Vaccines and Pediatrics, and Genetics Institute.

The Food and Drug Administration's (FDA) draft guidance language from the Federal Register notice is italicized in this letter and identified by line number(s). Our suggestions for revised language appear in standard type.

General Comments:

The Agency's draft guidance imposes additional regulatory burden on applicants in reporting changes to an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). Examples of these increased reporting requirements are given herein. It is our opinion that these new regulatory requirements are beyond the intent of Congress, when it drafted and approved the "Food and Drug Administration Modernization Act of 1997" (FDAMA). We ask the Agency to revise the draft guidance to remove the additional regulatory burdens and issue a guidance in keeping with Congress' intent.

We applaud the Agency in drafting a guidance to exemplify reporting categories for changes to drug products and drug substances. Examples of changes and their classification in FDAMA's language as "major" and the guidance's language as "moderate" and "minor" (*i.e.*, FDAMA's "other manufacturing changes") are helpful. The guidance, when revised to remove increased regulatory burdens, will assist both applicants and Agency reviewers in classifying changes for reporting to NDAs and ANDAs.

Specific Comments:

***Lines 32-34**: To the extent that the recommendations on reporting categories in this guidance, when finalized, are found to be inconsistent with prior published guidance, such as the SUPACs, the recommended reporting categories in such prior guidance will be superseded by this guidance.*

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The Agency should clarify that its policy is to retain in this guidance the reporting requirements in the SUPAC guidances, which give regulatory relief. It should be stated that the Agency does not intend to impose more stringent reporting requirements for the changes addressed by the SUPAC guidances, but rather, the Agency will revise the SUPAC guidances to be in conformance with FDAMA's language and to further reduce reporting requirements consistent with the revised guidance. This clarification would give comfort to applicants that the work to develop the SUPAC guidances will not be undone and that these guidances may continue to be used as references until they are revised.

***Lines 64-68**: Also, if FDA informs the applicant within 30 days of receipt of the supplement that information required under21 CFR 3 14.70(c)(4) is missing, distribution must be delayed until the missing information is provided and FDA determines that the additional information is in compliance with this section of the regulations (21 CFR 314.70(c)(5)(ii)).*

If the Agency determines that information is missing and the change can not be put into effect, and, if the applicant gives the missing information to the Agency, then FDA should expedite review of the amended filing. The Agency should re-respond to the applicant within no more than 30 days from receipt of the missing information that the Supplement-Changes Being Effected in 30 Days is acceptable for review and distribution of the product may begin.

Rationale: The guidance specifies no requirement for the Agency to act in a timely manner in this instance.

***Lines 70-73**: If after review FDA disapproves a changes being effected in 30 days supplement or changes being effected supplement, FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change (21 CFR 3 14.70(c)(7)).*

The Agency should clarify that, if an applicant submits a "Supplement-Changes Being Effected" (CBE) Supplement and FDA disapproves the CBE-30 Day or CBE supplement and requires this to be a prior-approval supplement, then the Agency will perform an "Expedited Review" of this prior approval supplement.

Rationale: An applicant may have followed all applicable regulations and guidances and submitted the CBE supplement in good faith. If FDA adds a new requirement unknown to the applicant, then the Agency should work rapidly to resolve the issue, especially if product, subject to the CBE change, is in distribution.

***Lines 79-84**: Under 21 CFR 3 14.70(e), an applicant may submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol must be submitted as a prior approval supplement (21 CFR 314.70(e)). FDA intends to issue separate guidance(s) on comparability protocols.*

A comparability protocol should be submitted as a "Supplement-Changes Being Effected in 30 days."

Rationale: This reporting requirement is to provide for a reduction in regulatory burden. It should be in the interest of the applicant and the Agency to further reduce regulatory burdens, wherever possible. Comparability protocols offer an outstanding means of accomplishing this goal. Reducing the time frame for review of a comparability protocol would bring much needed regulatory relief.

To help speed the utility of comparability protocols, the Agency should commit to issuing a guidance on developing them within six months of publishing the revised guidance on Changes to an Approved NDA or ANDA. Input from industry groups, working in partnership with the Agency, is highly recommended in developing the Comparability Protocol guidance.

The Agency should also revise regulations under **21 CFR 314.50(d) Content and Format of an Application** to permit and encourage the addition of comparability protocols to original applications. The addition of a comparability protocol to an application post-approval should not be the Agency's sole means of permitting this mechanism for regulatory relief.

***Lines 109-112**: For each change, the supplement or annual report must contain information determined to be appropriate by FDA and include the information developed by the applicant in validating (assessing) the effects of the change (section 506A of the Act).*

Delete the words "must contain information determined to be appropriate by FDA and" to read: For each change, the supplement or annual report include the information developed by the applicant in validating (assessing) the effects of the change (section 506A of the Act).

Rationale: The statement "must contain information determined to be appropriate by FDA and." is ambiguous, namely, whether the appropriateness is "predetermined," "post-determined" or both, by the FDA.

***Lines 141-145**: For example, evaluation of changes in the impurity or degradant profile could first involve profiling by high pressure liquid chromatography (HPLC) and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.*

Delete the words "high pressure liquid" and add the terms "TLC, GC, or other methods" to read: For example, an evaluation of changes in the impurity or degradant profile could first involve profiling by chromatography (HPLC, **TLC, GC, or other methods**) and then, ...

Rationale: The Agency should not imply by its example that HPLC is the only way of determining impurity and degradation profiles. Other chromatographic techniques may give equal or better profiling of related substances.

***Lines 151-153**: If guidance for information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff should be consulted.*

Substitute "should be consulted" with "may be consulted" to read: If guidance for information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff **may be consulted**.

Rationale: "Should" implies that it is Agency policy for applicants to consult with FDA for information requirements to support a change. Applicants should use their best judgment in deciding, when consultation with the FDA is needed.

***Lines 168-169**: Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product.*

We recommend the FDA define the term "adverse effect." For example, adverse effect may mean failure to meet established acceptance criteria.

***Lines 249-252**: 1. A move to any site, except one used to manufacture or process a drug substance intermediate, when the new facility has never been inspected by FDA for the type of operation that is being moved or the type of operation being moved used to be performed at the new facility, but at some time it had been discontinued and is now being restarted.*

Delete the words "or the type of operation being moved used to be performed at the new facility, but at some time it had been discontinued and is now being restarted." to read: A move to any site, except one used to manufacture or process a drug substance intermediate, when the new facility has never been inspected by FDA for the type of operation that is being moved.

Rationale: This phrase is vague and ambiguous from the meaning of both "type of operation" and "at some time."

***Lines 277-279**: 6. Except for modified release solid oral dosage form products, a move to a site on a different campus for the primary packaging of a drug product that falls within the scope of examples 4 or 5 (above).*

Move the words "except for modified release solid oral dosage form products:" to end of sentence to read: A move to a site on a different campus for the primary packaging of a drug product that falls within the scope of examples 4, except for modified release solid oral dosage form products, or 5 (above).

Rationale: For clarification of the exception intended.

***Lines 288-291**: b. A move to a site on the same campus (e.g., building changes) or within a single facility (e.g., room changes) for the manufacture or processing of sterile drug substance or drug product that is not otherwise listed as a major change.*

Add the word "sterile" in front of "drug product" to read: A move to a site on the same campus (e.g., building changes) or within a single facility (e.g., room changes) for the manufacture or processing of sterile drug substance or **sterile** drug product that is not otherwise listed as a major change.

Rationale: For clarification.

***Lines 314-315**: 1. A move to a new secondary packaging site on the same (i.e., contiguous) or different campus,*

Delete words "the same (i.e., contiguous) or" to read: A move to a new secondary packaging site on a different campus,

Rationale: This is an increase in regulatory burden that is not justified.

***Line 316**: 2. A move to a new labeling site on the same or different campus.*

Delete the words "the same or" to read: A move to a new labeling site on a different campus

Rationale: This is an increase in regulatory burden that is not justified.

***Line 317**: 3. A move to a new testing site on the same campus.*

Delete line 317.

Rationale: This is an increase in regulatory burden that is not justified.

***Lines 319-322**: 4. A move to a site on the same campus (i.e., building changes) for the manufacture or processing (including primary packaging) of nonsterile drug substance, in-process material, or drug product, except as otherwise listed.*

Delete lines 319-322.

Rationale: This is an increase in regulatory burden that is not justified.

***Lines 324-326**: 5. Site changes within a single facility (e.g., room changes) for the manufacture or processing of drug product or in-process material, or primary packaging, except as otherwise listed for sterile drug products?*

Delete lines 324-326.

Rationale: This is an increase in regulatory burden that is not justified.

***Lines 333-334**: 7. A change in the simple floor plan that does not affect the production process or contamination precautions. This includes a facility "build-out."*

Delete lines 333-334.

Rationale: This is an increase in regulatory burden that is not justified.

***Lines 335-336**: 8. Improvements to manufacturing areas that provide greater assurance of quality.*

Delete lines 335-336.

Rationale: This is an increase in regulatory burden that is not justified.

***Lines 370-372**: 2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:*

Insert the word "adversely" before "affect" to read: Changes that may **adversely** affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

Rationale: The only criterion for a change affecting sterility assurance of a sterile drug product or sterile drug substance that should be regarded as a major change should be one, which adversely affects sterility assurance. Changes, which positively affect sterility assurance, should be regarded as moderate or minor changes.

***Lines 408-409**: 4. Any fundamental change in the manufacturing process or technology from that which is currently used by the applicant. For example:*

Insert the words "for a drug product" after the word "technology" to read: Any fundamental change in the manufacturing process or technology **for a drug product** from that which is currently used by the applicant. For example:

Rationale: For clarification.

***Line 413**: Filtration to centrifugation or vice versa.*

Add the words "for a drug substance" to read: Filtration to centrifugation or vice versa **for a drug substance.**

Rationale: For clarification.

***Lines 418-420**: Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.*

Replace the word "may " with the word "adversely" to read: Changes in the synthesis or manufacture of the drug substance that **adversely** affect its impurity profile and/or the physical, chemical, or biological properties.

Rationale: Changes in the synthesis or manufacture of a drug substance that improve the impurity profile should be treated as moderate or minor changes.

***Lines 442-444**: Filtration process changes that provide for a change from single to dual product sterilizing filters, or for repeated filtration of a bulk.*

Delete lines 442-444.

Rationale: This kind of change should be treated as a GMP validation issue.

***Lines 450-456**: When terminal sterilization autoclaves are replaced, the range of thermal input (F-value) for the load should be demonstrated to fall within the range previously validated, such that the minimum thermal input does not reduce sterility assurance and the maximum thermal input does not reduce product stability or adversely affect container and closure integrity.*

Delete lines 450-456.

Rationale: This should be considered as a GMP validation issue.

***Lines 457-461**: Changes in scale of manufacturing for aseptically processed products that do not require additional aseptic filling shifts or do not increase bulk solution storage time by more than 50 percent beyond the validated limits in the approved application.*

Substitute the word "increases" for "changes" to read: **Increases** in scale of manufacturing for aseptically processed products that do not require additional aseptic filling shifts or do not increase bulk solution storage time by more than 50 percent beyond the validated limits in the approved application.

Rationale: Only increases in scale would be expected to increase bulk solution storage time.

***Lines 483-484**: 2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.*

Delete the word "minor" to read: A change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.

Rationale: Any change to an existing code imprint, e.g., changing from a numeric to alphanumeric code, addition of a logo or identifying icon, changes to names, should be considered a minor change and therefore should be treated as an annual reportable change.

***Lines 558-562**: a. An addition to a specification or changes in methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, purity, or potency which it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.*

We recommend that these kinds of changes be treated as minor changes. This would be consistent with the regulatory treatment of change identified in line 577: "Tightening of acceptance criteria."

***Lines 567-571**: 1. Any change made to comply with an official compendium that is consistent with FDA requirements and that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.*

Delete all words after compendium to read: Any change made to comply with an official compendium.

Rationale: Upon the establishment of a USP monograph of an article, for which FDA participates in the USP approval process, USP criteria should apply for all applicants. There should be no need for an applicant to file any supplement for a change made to comply with an official compendium. This will allow a level playing field for innovator and generic firms, when referencing USP criteria in their applications. FDA's proposed language represents an increased regulatory burden for applicants.

***Lines 584-585**: 5. Tightening of specifications for existing reference standards to provide increased assurance of product purity and potency.*

Delete lines 584-585

Rationale: Reference standards specifications should not be subject to filing requirements. This represents an increased regulatory burden for applicants.

***Lines 604-605**: (4) changes may affect product sterility assurance;*

Add the word "adversely" before "affect" to read: (4) changes may **adversely** affect product sterility assurance;

Rationale: Changes that positively affect product sterility assurance should not be treated as major changes. See comment under Lines 370-372.

***Line 626-627**: 4. For sterile products, any other change that may affect product sterility assurance such as:*

Add the word "adversely" before affect to read: 4. For sterile products, any other change that may **adversely** affect product sterility assurance such as:

Rationale: Changes that positively affect product sterility assurance should not be treated as major changes. See comments under Lines 370-372.

***Lines 638-639**: Changes in the size and/or shape of a container for a sterile drug substance or sterile drug product.*

Move these examples to Moderate Changes.

Rationale: These kinds of changes should be considered moderate changes, if same materials of construction are used.

***Lines 661-662**: 2. A change in the size and/or shape of a container containing the same number of dose units, for a nonsterile solid dosage form.*

Replace the words "containing the same" with "and/or" to read: A change in the size and/or shape of a container **and/or** number of dosage units, for a nonsterile solid dosage form.

Rationale: The applicant should determine, if a change in the number of dosage units has minimal potential to have an adverse effect on the product. If so, the applicant should be permitted to change the number of dosage units in a container and treat this as a minor change.

***Lines 729-730**: 2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.*

The Agency should make it clear that the prior approval requirement applies only to labeling pharmacoeconomic claims.

***Line 735**: 6. Claims of superiority to another product.*

The Agency should make it clear that the prior approval requirement applies only to labeling superiority claims.

***Lines 736-737**: 7. Change in the labeled storage conditions, unless exempted by regulation or guidance.*

Replace the words "change in" with "relaxing" to read: **Relaxing** the labeled storage conditions, unless exempted by regulations or guidance."

Rationale: A change, which strengthens the labeled storage condition, should not be considered a major change.

***Lines 742-743**: (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product,*

Replace the words "and administration" with the words "administration and storage" to read: (3) adds or strengthens an instruction about dosage **administration and storage** that is intended to increase the safe use of the product.

Rationale: Addition of a storage statement, which strengthens the labeling, should be treated as a moderate change.

***Lines 751-752**: 3. Clarification of the administration statement to ensure proper administration of the product.*

Replace the word "statement" with "and storage statements" and add the words "and storage" after the word "administration" to read: "clarification of the administration and **storage statements** to ensure proper administration **and storage** of the product."

Rationale: Addition of a storage statement, which strengthens the labeling, should be treated as a moderate change.

Lines 776-777: *2. Changes that may affect product sterility assurance (21 CFR 314.70(b)(2)(iii)).*

Insert the word "adversely" before the word "affect" to read: Changes that may **adversely** affect product sterility assurance (21 CFR 314.70(b)(2)(iii)).

Rationale: Changes that may positively affect sterility assurance should not be treated as major changes. See comments under lines 370-372.

Line 778: *3. Approval of a comparability protocol (21 CFR 3 14.70(e)).*

A comparability protocol should be submitted as a "Supplement-Changes Being Effected in 30 Days." Rationale for this reporting requirement is a reduction in regulatory burden. See comments under lines 79-84.

Lines 794-799: *3. Reference standards: Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application. Tightening of specifications for existing reference standards to provide greater assurance of product purity and potency.*

Delete lines 794-799.

Rationale: Reference standards specifications should not be subject to filing requirements. This represents an increased regulatory burden for applicants.

On behalf of Wyeth-Ayerst Laboratories and its affiliates, we appreciate the opportunity to comment on this important guidance.

Sincerely,

WYETH-AYERST LABORATORIES

Vern DeVries

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VDV/KFB/las:guidancecomments